ORIGINAL ARTICLE

Effect of diet low in advanced glycation end products on appetite, body composition, and brown adipose tissue markers in patients with coronary artery disease treated with angioplasty: A randomized controlled trial

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Background: Recent changes in dietary habits have resulted in increased intake of advanced glycation end products (AGEs), which are known to have a predominant contribution to the pathogenesis and complications of coronary artery disease (CAD). AGEs are also thought to induce weight gain by affecting appetite, energy expenditure, and brown adipose tissue (BAT). Here, we investigated whether the restriction of dietary AGEs could affect appetite, body composition, anthropometric indices, and BAT-derived markers in CAD patients treated with angioplasty. **Materials and Methods:** Forty-two stented CAD patients were randomly allocated into two groups that received either a low-AGEs or a control diet for 12 weeks. At baseline and postintervention, fasting blood samples were analyzed for total AGEs, nesfatin-1, and BAT-derived markers (fibroblast growth factor 21 and neuregulin 4). Subjective appetite ratings and body composition were evaluated using the Visual Analog Scale (VAS) and bioelectric impedance analysis. Anthropometric indices, including fat mass index (FMI), abdominal volume index (AVI), and body adiposity index (BAI), were calculated through the relevant formula. **Results:** Restricting dietary AGEs for 12 weeks could cause a significant reduction in weight, FMI, AVI, and BAI ($P < 0.05$) compared to the comparison group. In addition, VAS data analyses indicated a significant decrease in the sense of hunger and prospective food intake ($P < 0.05$) in the intervention group compared to the comparison group. No significant difference was seen in the measured biochemical markers between the two groups. **Conclusion:** This study indicated that the low-AGEs diet could decrease appetite, weight, and anthropometric indices in stented CAD patients.

Key words: Advanced glycation end products, appetite, brown adipose tissue, coronary artery disease, nesfatin-1

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INTRODUCTION

Overweight/obesity, a premier public health issue worldwide, is highly prevalent in patients with established coronary artery disease (CAD). Over the past two decades, the proportion of CAD patients with central obesity increased from 32.5% to 61.3%.[1] Obesity is not only an independent cardiovascular risk factor but also it is associated with other traditional cardiovascular risk factors.[2] Weight loss of around 5%–10% can lead to a clinically meaningful cardiovascular risk reduction.[3]

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Advanced glycation end products (AGEs) are a heterogeneous group of constituents with prooxidant and cytotoxic properties formed through the Maillard reaction, the nonenzymatic addition of reducing sugars to proteins, lipids, or nucleic acids. Animal-source foods, especially when prepared by high-heat cooking methods such as roasting, grilling, broiling, and frying, contain high amounts of AGEs.[4] AGEs have a fundamental role in CAD pathogenesis through receptor-dependent and independent mechanisms. Apart from AGEs-induced crosslinking with macromolecules such as collagen and elastin, which alters their structure and function, activating receptors for AGEs (RAGE) on AGEs binding triggers intracellular cascades that result in oxidative stress and inflammation.[5]

Growing evidence also suggests that AGE-RAGE signaling may contribute to weight gain and obesity, which can complicate CAD management. AGEs can enhance appetite by increasing foodstuffs' flavor, smell, and appearance.[6] In addition, RAGE is proposed as a critical regulator of weight gain and adiposity since it affects energy expenditure and the browning process, a process in which brown adipose tissue (BAT)-like phenotype is induced in white adipose tissue (WAT) in response to various stimuli.[7,8] BAT has a protective role in energy balance by dissipating energy as heat and increasing energy expenditure.[9] During BAT activation and the browning process, the secretion of BAT-derived endocrine factors (batokines), such as fibroblast growth factor 21 (FGF21) and neuregulin 4 (NRG4) is increased.[10]

Since the diet is the primary exogenous source of AGEs contributing to the total body AGEs pool,[11] dietary AGEs restriction would probably modulate different pathways involved in the progression of obesity and appears to be beneficial independently from the consumption of standard energy-restricted diets. In addition, reduced AGEs intake could be effective in CAD patients, for whom AGEs can cause more clinical outcomes. Accordingly, the present study was designed to investigate whether consuming a low-AGEs diet without calorie restriction can have beneficial effects on appetite, body composition, weight, anthropometric indices, and BAT-derived endocrine markers in CAD patients.

SUBJECTS AND METHODS

Subjects

Patients aged 50–65 years with a body mass index (BMI) of 18.5–35 kg/m^2 treated with angioplasty because of having 1 or 2 blocked arteries were assessed for eligibility. Patients were excluded from participation if they had diabetes, chronic kidney disease, cancer, thyroid, autoimmune diseases, familial hypercholesterolemia or hypertriglyceridemia, and a history of myocardial infarction, stroke, or angioplasty during the past 3 months. In addition, we excluded patients who were current smokers, consumed multivitamins, mineral or anti-oxidant supplements, or followed any weight loss diets during the past 3 months before angioplasty and women before menopause.

All patients' records that underwent angioplasty at Tehran Heart Center from September 2020 to June 2021 were prescreened, and eligible patients were invited to attend an information meeting. Patients were screened again at the first meeting, and 42 volunteers started the dietary intervention. All volunteers provided written informed consent before participation. The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1398.334) and registered at the Iranian Registry of Clinical Trials (IRCT20131125015536N10).

Study design

This study was a randomized controlled clinical trial with parallel groups. To randomly assign eligible patients to either the low-AGEs or the comparison groups, we used a computer-based generated random sequence based on sex-stratified permuted block randomization with the random block size of 2 and 4.

Data regarding anthropometric characteristics, body composition, and appetite sensation were collected at baseline and the end of the 12th week. Furthermore, 10 ml of blood was obtained from each participant after an overnight fast for biochemical analyses. All patients received their drugs and treatments during the study, and no changes were made to the health-care protocol of the hospital.

Dietary intervention and follow-up

Both groups' diets were similar in macronutrient percentage and designed to meet American Heart Association (AHA) and National Cholesterol Education Program (NCEP) dietary recommendations for CVD but differed in the AGEs content. AHA/NCEP recommendations in CVD patients include a total fat intake of 25%–30% of total energy (<20% monounsaturated fatty acid [MUFAs], <10% polyunsaturated fatty acid [PUFAs], and <7% saturated fatty acid [SFAs]), 15% protein, 50%–60% carbohydrates, and restriction of added sugars (<100 Kcal/d for women and <150 Kcal/d for men), sodium (≤2300 mg/d), and cholesterol (≤200 mg/d). Participants were instructed on the proportions and types of foods they should consume from different food groups to achieve the required macronutrient content. They were encouraged to eat to their appetite and select portion sizes that they felt were appropriate for them.

Both groups received all AHA/NCEP dietary recommendations orally and in writing. The low-AGEs group was also instructed on how to choose and prepare their foods to reduce the AGEs content of the diet. The instructions included thorough guidance on the cooking process (methods, temperature, and duration) and a food choice list. The low-AGEs group was instructed to stew, steam, boil, or poach their foods and avoid frying, baking, roasting, or grilling. The food choice list consisted of foods with high AGEs content that are not allowed and foods with lower AGEs content that are accepted for consumption. In addition, the participants were given some predefined main meals and snacks. To promote dietary compliance, telephone calls were made by the dietitian to emphasize dietary instructions every 2 weeks during the study. In addition, patients could call the dietitian whenever they had any questions about the intervention.

Measurements

Anthropometry and body composition

Body weight, height, and waist circumference were measured in fasting state using a portable digital scale (Seca, Germany), a vertical wall-mounted stadiometer (Seca, Germany), and a flexible measuring tape.

The body composition was assessed using multi-frequency (1, 5, 50, 250, 500, and 1000 kHz) bioelectric impedance analysis (InBody770, Korea). The volunteers were asked to restrain from physical activity for 8 h and avoid coffee and alcohol consumption 24 h before the test. Furthermore, they were recommended to drink 1–2 glasses of water 3 h before the test to stay hydrated.

Measurement of biochemical markers

Fasting blood samples were collected at the baseline and end of the trial, and serum was isolated. Serum concentrations of total AGEs, nesfatin-1, FGF21, and NRG4 were determined using enzyme-linked immunosorbent assay kits (Crystal Day, China).

Appetite estimation

Appetite sensation was assessed in the fasting state by Visual Analog Scale (VAS), a reliable and reproducible measure of appetite in the research setting. VAS consists of a 100 mm line anchored from "not at all" to "extremely" and evaluates the four subjective senses of hunger, fullness, desire to eat, and prospective food consumption (PFC). Participants were instructed to mark each line corresponding to their appetite level. The score of each question was quantified by measuring the distance between the mark and the beginning of the line. The composite appetite score (CAS) was calculated using the following formula:[12]

$$CAS = (\text{desire-to-eat} + \text{hunger} + [100 - \text{fullness}] + PFC)/4$$

Dietary intake and physical activity

The assessment of dietary intake was based on three 24-h dietary recalls (two working days and one weekend day) obtained from all participants in the 1st and 12th week of intervention. Then, the average daily energy and macronutrient intake based on each subject's food recalls was calculated using Nutritionist IV software modified for Iranian foods. In addition, the AGEs content of each recall was estimated using a database that lists the AGEs values of about 560 foods.[13]

Physical activity was assessed through patients' records. Subjects were educated to record the type and duration of all their activities within 24 h for 2 days (one working day and one weekend day) at weeks 1 and 12 of the intervention. Then, the mean of physical activity for each subject was calculated by metabolic equivalents of the task determined previously for each activity.[14] Furthermore, participants were required not to change their physical activity throughout the trial. The validity of this method to assess physical activity has been investigated in previous studies.[15,16]

Indices calculation

BMI was calculated as weight (kg) divided by height squared in meters. Fat mass index (FMI) was calculated by body fat mass divided by height squared. Abdominal volume index (AVI) and body adiposity index (BAI) were estimated based on the following formulas developed previously:[17,18]

$$BAI = \text{hip circumference}/\text{height}^{1.5} - 18$$

$$AVI = (2\ \text{cm} \times [\text{waist}]^2 + 0.7\ \text{cm} \times [\text{waist} - \text{hip}]^2)/1000$$

Statistical analysis

The primary outcomes were weight and waist circumference, and the secondary outcomes were anthropometric indices (FMI, AVI, and BAI), bioelectric impedance analysis variables, and serum biomarkers. Considering the type one error of 0.05 and the type 2 error of 0.20, the sample size required for each group was calculated as 21, which provides the test power of 80% for an effect size as large as 0.6, and 42 subjects entered the study.

All analyses were performed using SPSS 24.0 (SPSS, Inc., Chicago, IL, USA). The per-protocol approach was applied for data analysis. The Kolmogorov–Smirnov test was used to examine the normal distribution of variables. Except for some variables of VAS, including satiety, desire to eat, and PFC and visceral fat level that did not have a normal distribution ($P < 0.05$), the distribution of the other studied variables was normal ($P > 0.05$). For variables with nonnormal distribution, log transformation was conducted. Differences in qualitative and quantitative

variables between the low-AGEs and comparison groups were determined using Chi-square and independent sample *t*-tests, respectively. The significance of changes during the intervention within each group was detected by paired *t*-test. Multivariate analysis of covariance was used to test if the change from baseline in the outcome variable differed significantly by the group while baseline values of the outcome variable were adjusted as covariates. A two-tailed significance $P < 0.05$ was set for all analyses.

RESULTS

Forty-two volunteers started the intervention, and 39 completed the trial and were included in the final statistical analysis [Figure 1]. The baseline characteristics of the participants in both groups are depicted in Table 1. At the study initiation, there was no significant difference between the two groups regarding age, sex, weight, BMI, waist circumference, serum concentration of total AGEs, and other confounding variables ($P > 0.05$), suggesting adequate randomization.

Weight and BMI decreased in both groups during the intervention, but the reduction was more in the low-AGEs group than in the comparison group [$P = 0.02$ and $P = 0.06$ for weight and BMI, respectively; Table 2]. Although waist circumference, fat mass, and visceral fat level were decreased within both groups, and the reduction was more in the low-AGEs group, the difference between groups was not statistically significant ($P > 0.05$). Other variables of body composition did not differ between groups throughout the study. As shown in Table 2, FMI, BAI, and AVI were decreased with statistical significance in the low-AGEs group compared to the comparison group ($P = 0.04$, $P = 0.02$, and $P = 0.048$, respectively).

Dietary data analysis showed that all patients complied with AHA/NCEP recommendations. Total intakes of

Table 1: Subject characteristics at baseline

Characteristic	Groups		*P**
	Low-AGEs group (*n*=20)	Comparison group (*n*=19)	
Age (years)	58.2±1.4	56.6±1.2	0.39
Women, *n* (%)	4 (19)	4 (19)	1
Married, *n* (%)	19 (90.5)	17 (80.9)	0.38
Education, *n* (%)			0.46
Elementary	6 (28.6)	7 (33.3)	
Undergraduate	10 (47.6)	12 (57.1)	
Graduate	5 (23.8)	2 (9.5)	
Weight (kg)	81.2±2.1	82±2.3	0.82
BMI (kg/m^2)	28.5±0.7	29.3±0.8	0.43
Waist circumference (cm)	96.8±2	101.5±2	0.11
Serum total AGEs (ng/L)	648.7±144.4	581.9±124.1	0.73
SBP	12.5±0.2	12.2±0.1	0.25
DBP	7.5±0.5	7.7±0.1	0.26

Values are reported as mean±SEM. *All *P* values are calculated by independent *t*-test except for sex and education which were calculated by Chi-square test. BMI=Body mass index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; AGEs=Advanced glycation end products; SEM=Standard error of mean

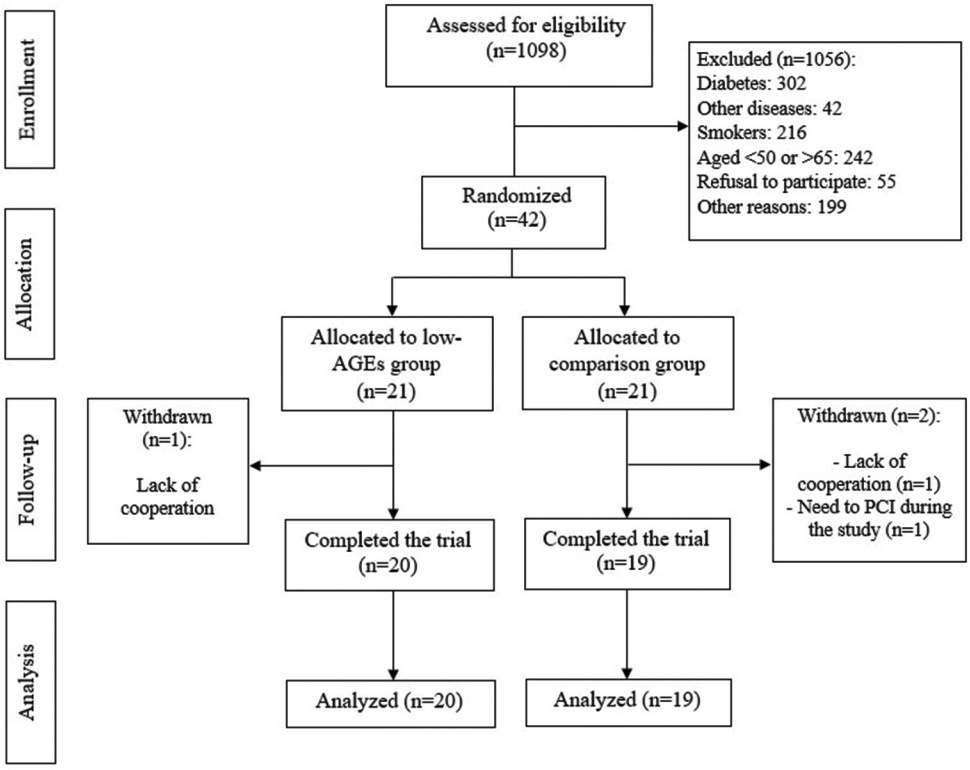

Figure 1: Flow diagram of the participants

macronutrients, the amount of fiber, added sugars, sodium, and cholesterol were all within the recommended range by AHA/NCEP. In addition, they were similar between groups throughout the dietary intervention. The total energy intake was significantly decreased in the low-AGEs group from baseline to the end of the trial ($P = 0.05$), although the difference in energy intake between the two groups was not statistically significant [$P = 0.14$; Table 3].

As expected, the two groups had a significant difference in AGEs intake [$P < 0.001$; Table 3]. Furthermore, the AGEs intake in the low-AGEs group was significantly

Table 2: Anthropometric measurements and body composition analysis of participants

Variables	Low-AGEs group (*n*=20)			Comparison group (*n*=19)			*P*†
	Baseline	Post-intervention	*P**	Baseline	Post-intervention	*P**	
Weight (kg)	81.2±2.1	78.6±2.2	<0.001	82±2.3	81±2.3	0.03	0.02
BMI (kg/m^2)	28.5±0.7	27.6±0.7	0.001	29.3±0.8	29±0.8	0.03	0.06
WC (cm)	96.8±2	94±2	0.002	101.5±2	100.1±2.3	0.06	0.22
FM (kg)	24.7±1.6	22.4±1.6	0.001	27.9±1.6	26.6±1.7	0.02	0.16
PFM (%)	30.4±1.7	28.5±1.7	0.001	33.9±1.4	32.6±1.6	0.03	0.37
FFM (kg)	56.4±1.9	56.1±1.9	0.29	54±1.6	54.3±2.1	0.16	0.1
PFFM (%)	69.6±1.7	71.5±1.7	0.001	66.1±1.4	67.4±1.6	0.03	0.37
TBW (kg)	41.5±1.4	41.3±1.4	0.32	39.8±1.2	40.1±1.3	0.16	0.12
VFL	11.2±0.9	10.1±0.9	0.001	13±0.9	12.1±1	0.004	0.53
FMI	8.8±0.7	7.9±0.7	<0.001	10.1±0.6	9.6±0.7	0.02	0.04
AVI	18.9±0.9	17.6±0.8	<0.001	20.8±0.8	20.2±0.9	0.07	0.048
BAI	29.1±1	28.4±1	0.001	29.8±0.8	29.6±0.8	0.06	0.02

*Calculated by paired *t*-test; †Calculated by ANCOVA, adjusted for the baseline values. Values are reported as mean±SEM. BMI=Body mass index; WC=Waist circumference; FM=Fat mass; PFM=Percentage of FM; FFM=Fat free mass; PFFM=Percentage of FFM; TBW=Total body water; VFL=Visceral fat level; FMI=Fat mass index; AVI=Abdominal volume index; BAI=Body adiposity index; AGEs=Advanced glycation end products; SEM=Standard error of mean; ANCOVA=Analysis of covariance

Table 3: Physical activity and nutritional intake of participants

Variables	Low-AGEs group (*n*=20)			Comparison group (*n*=19)			*P*†
	First week	12th week	*P**	First week	12th week	*P**	
Energy (Kcal/day)	1980±68	1847±82	0.05	2066±104	2029±89	0.72	0.14
Protein							
g/day	80.3±5	73.2±3.8	0.15	82.9±5.9	75.1±3.7	0.17	0.72
Percentage of energy	16.2±0.9	15.9±0.7	0.69	16.1±1	14.8±0.6	0.17	0.24
Carbohydrate							
g/day	276±15.1	264.3±16.2	0.24	290.2±21.7	301.7±18.6	0.58	0.14
Percentage of energy	55.8±2	57.2±1.8	0.28	56.2±2.3	59.5±2	0.15	0.44
Fat							
g/day	61.6±4.3	55.2±4.2	0.1	63.7±5.5	58±4.1	0.16	0.63
Percentage of energy	28±2.1	26.9±1.9	0.45	27.7±2.3	25.7±2	0.37	0.72
PUFA							
g/day	18.3±1.5	16.3±1.5	0.28	17.7±2.1	18±1.8	0.8	0.48
Percentage of energy	8.4±0.7	7.9±0.6	0.53	7.8±0.9	8.2±0.9	0.66	0.81
MUFA							
g/day	26.4±1.9	23.2±1.8	0.11	26.1±2.5	22.6±1.9	0.1	0.83
Percentage of energy	12.2±1	11.5±0.8	0.37	11.5±1.1	10.3±1	0.22	0.35
SFA							
g/day	12.5±1.3	12.1±1.3	0.71	15.2±1.5	13.2±0.9	0.15	0.49
Percentage of energy	5.7±0.6	6.1±0.7	0.52	6.5±0.5	5.9±0.3	0.18	0.77
Sugar (Kcal/day)							
Men	64.9±9.6	74.9±12.3	0.32	77.5±17.7	77.7±15.3	0.98	0.88
Women	27.5±4.8	38.2±16.1	0.63	48.5±16.9	31±10.5	0.31	0.72
Fiber (g/day)	17±1.3	19.5±1.5	0.12	15.3±1.1	17.3±0.8	0.17	0.22
Cholesterol (mg/day)	206.2±23.8	172.2±24.6	0.3	207.4±20.5	177.6±15.8	0.08	0.87
Sodium (mg/day)	1913±74	1861±99	0.52	1945±74	1820±88	0.28	0.76
Dietary AGEs (KU/day)	8378±987	6986±799	0.007	19518±2572	19399±2539	0.89	<0.001
Physical activity (MET-h/day)	33.3±1	33.2±1.1	0.87	31.5±1.1	32.1±1.1	0.5	0.84

*Calculated by paired *t*-test; †Calculated by independent *t*-test. Values are reported as mean±SEM. PUFA=Polyunsaturated fatty acid; MUFA=Monounsaturated fatty acid; SFA=Saturated fatty acid; AGEs=Advanced glycation end products; SEM=Standard error of mean

reduced at the end of the study compared to the beginning ($P = 0.007$).

In the low-AGEs group, the sense of hunger ($P = 0.04$), desire to eat ($P = 0.03$), and CAS ($P = 0.04$) were decreased, and the satiety score ($P = 0.01$) increased significantly after the intervention compared to the baseline [Table 4]. No changes in appetite scores occurred in the comparison group. Between-group analysis revealed that the low-AGEs diet could significantly decrease the sense of hunger ($P = 0.03$) and PFC ($P = 0.01$) and also caused a notable reduction in CAS ($P = 0.06$).

The results of biochemical markers are indicated in Table 5. The serum concentration of nesfatin-1, NRG4, and FGF21 was not significantly changed within or between groups after the intervention.

DISCUSSION

In this study, restriction of dietary AGEs for 12 weeks significantly decreased weight and caused a notable reduction in BMI postintervention. Many clinical trials have assessed the effect of a low-AGEs diet on weight, BMI, and WC, and their findings are controversial. While some studies have shown the reducing effect of the low-AGEs diet on weight and BMI,[19,20] others found no effect.[21,22] Meta-analysis of prior studies has depicted that consumption of the low-AGEs diet can significantly reduce weight and BMI compared to the high-AGEs diet, with a more pronounced effect in studies with a duration of more than 8 weeks,[23] which is consistent with our findings. In our study, despite the two-fold decrease in WC, the difference between groups was not significant. Similarly, the mentioned meta-analysis found no significant difference in WC between the low and high-AGEs diets.[23]

It has recently been hypothesized that AGEs play a putative role in the pathogenesis of obesity by their ability to increase appetite and energy intake through enhancing sensory-stimulating properties of foodstuffs.[6,24] Furthermore, a growing body of evidence highlighted the role of AGEs in promoting insulin resistance and activating pro-inflammatory pathways.[25,26] Considering the central role of insulin in regulating energy balance and the implication of pro-inflammatory cascades in mediating hypothalamic dysregulation of energy balance, insulin resistance, and inflammation may represent further potential mechanisms supporting the ability of AGEs to disrupt hypothalamic control of energy balance leading to body weight gain.[27] Several studies have indicated the effect of dietary AGEs limitation on improving insulin resistance and reducing inflammatory markers.[21,28] Therefore, the reducing effects of the low-AGEs diet on weight and BMI might be attributed to its beneficial impacts on insulin resistance and inflammation, which is more notable in overweight and obesity.

In the present study, we also evaluated the effects of the low-AGEs diet on anthropometric indices (FMI, AVI, and BAI). Most previous studies used BMI as the primary outcome because CDC/WHO currently recommends it for classifying overweight and obesity. However, epidemiological studies have questioned the capacity of BMI to predict cardiovascular risk due to its limitation in distinguishing excess adipose tissue from lean mass.[29,30] BMI calculation does not consider intra-abdominal or visceral adipose tissue, which its accumulation is closely associated with increased CVD risk.[31] Therefore, simple-to-use anthropometric indices have been recently developed as a surrogate or complementary measure to estimate central obesity more accurately. FMI is a potential indicator of

Table 4: Effect of dietary intervention on subjective appetite scores

Variables	Low-AGEs group (*n*=20)			Comparison group (*n*=19)			*P*†
	Baseline	Post-intervention	*P**	Baseline	Post-intervention	*P**	
Hunger	40.2±5.7	29.1±4.8	0.04	32.9±5	40.5±5.3	0.24	0.03
Satiety	41.4±4.1	52.3±4.3	0.01	45.2±5.8	49±5	0.46	0.37
Desire to eat	61.5±4.4	52.4±4.5	0.03	64.3±5.1	64.8±3.3	0.43	0.12
PFC	67.9±4.7	65.7±4.9	0.48	71±7	80.2±5.2	0.07	0.01
CAS	58.9±4.4	50.8±3.9	0.04	53.4±4.2	57.4±3.6	0.4	0.06

*Calculated by paired *t*-test; †Calculated by ANCOVA, adjusted for the baseline values. Values are reported are mean±SEM. ANCOVA=Analysis of covariance; PFC=Prospective food consumption; CAS=Composite appetite score; SEM=Standard error of mean

Table 5: Biochemical markers of participants at baseline and postintervention

Variables	Low-AGEs group (*n*=20)			Comparison group (*n*=19)			*P*†
	Baseline	Post-intervention	*P**	Baseline	Post-intervention	*P**	
Total AGEs (ng/L)	648.7±144.4	618±122.8	0.65	581.9±124.1	632.1±121.9	0.34	0.34
Nesfatin-1 (ng/mL)	13.6±4.4	14±3.7	0.71	7.7±2.3	8.8±2.2	0.1	0.83
NRG4 (ng/mL)	3.1±0.8	3±0.7	0.64	2.1±0.4	1.9±0.4	0.35	0.33
FGF21 (pg/mL)	318.8±68.6	297.3±66.3	0.39	246.8±47.4	231±40.1	0.55	0.88

*Calculated by paired *t*-test; †Calculated by ANCOVA, adjusted for the baseline values. Values are reported as mean±SEM. AGEs=Advanced glycation end products; NRG4=Neuregulin 4; FGF21=Fibroblast growth factor 21; SEM=Standard error of mean; ANCOVA=Analysis of covariance

body adiposity superior to BMI and PBF because of taking fat mass and height into account, which reduces the bias associated with BMI and PBF.[32,33] Previous research has highlighted the capability of FMI to predict metabolic syndrome and cardiovascular risk in young adults.[34] AVI, a reliable anthropometric tool that reflects the total volume of the abdomen by including WC and HC, has been used by researchers to indirectly estimate the visceral fat volume.[35] AVI sensitivity to evaluate fat deposition in viscera and associated metabolic abnormalities have been confirmed in prior studies.[36,37] Also, BAI is reported as another index that could be a valid predictor of body fat.[17] Despite no significant decrease in fat mass, the reduction in FMI, which adjusts fat mass for height, was significant between the two groups in our study. Furthermore, a significant decrease in AVI and BAI was observed in the low-AGEs group compared to the comparison group. Regarding these indices being a better indicator of visceral adipose tissue, restriction of dietary AGEs might improve metabolic disturbances associated with CAD through reduced visceral fat. Few prior trials have focused on changes in abdominal obesity, and most studies have assessed the relationship between indices and risk factors cross-sectionally based on one static measurement. But when it comes to chronic diseases like CAD, due to the impact of long-term accumulation of the risk factors, there is a need to evaluate the dynamic change of risk factors such as anthropometric indicators over time, which we tried to achieve in this research.

The percentage of macronutrient intake and the essential recommendations of AHA/NCEP guidelines (levels of SFA, MUFA, PUFA, cholesterol, added sugar, and sodium) were not different between the studied groups. However, dietary AGEs content was significantly lower in the low-AGEs group over the intervention period. Despite a falling trend of serum total AGEs concentration in the low-AGEs group throughout the study, this trend was not significant. Our results are consistent with those of other studies, which have either shown no changes in serum AGEs levels following intake of the low-AGE diet or have found decreases in plasma carboxy methyl lysine (CML) concentrations after a high-AGEs diet administration.[38,39] Interestingly, AGEs calculated from recalls and urinary AGEs had shown the expected changes in the mentioned studies. It has been suggested that measuring a combination of circulating, tissue, and excreted AGEs concentrations might better represent the total AGEs burden in the body since each measurement has its limitations.[19,39] AGEs are also characterized by complex structural and molecular heterogeneity, making it difficult to quantify them. Although various instrumental and immunochemical methods are used to measure AGEs, there is currently no gold standard method for AGEs quantification.[40]

In the present study, the low-AGEs diet decreased the sense of hunger, PFC, and CAS compared to the control diet. A recent animal study reported that an AGEs-rich diet could activate neuronal and hormonal signaling engaged in appetite regulation and energy homeostasis.[41] However, a human study found no changes in VAS appetite scores after consuming a high or low-AGEs meal.[42] The difference might be attributed to the different design of the mentioned study in which the acute response to dietary AGEs was assessed, whereas we evaluated the longer-term effect of dietary AGEs on subjective appetite sensations.

Our findings showed no changes in the serum concentration of nesfatin-1 by restriction of dietary AGEs. One of the mechanisms of appetite regulation that AGEs affect is hormones. Among appetite-regulating hormones, the effect of dietary AGEs on ghrelin has previously been investigated in a single-meal study which observed increased ghrelin response after a high-AGEs meal compared to a low-AGEs meal.[42] Until now, no study has assessed the relationship between AGEs and nesfatin-1 secretion. Appetite regulation and energy hemostasis are controlled by a very complex neuro-humoral system, which includes short-term and long-term signals, and many peripheral and central peptides are involved in this system.[43] Therefore, the lack of change in nesfatin-1 might be due to the compensatory effects of other peptides involved in this system, which were not investigated here.

One of our hypotheses was that the effects of AGEs restriction on weight loss might occur through increased energy expenditure by BAT. Our findings showed no effect of the low-AGEs diet, an influential factor in reducing RAGE signaling, on BAT-derived markers. Until now, no human trial has tested the relationship between RAGE and BAT. Animal evidence suggests a link between RAGE and high-fat diet (HFD)-induced obesity and subsequent metabolic dysfunction due to enhanced concentration of RAGE ligands such as CML and methylglyoxal which are known AGEs.[7] A recent study in mice showed that RAGE deletion increased the expression of uncoupling protein-1 (UCP-1), usually only expressed in BAT, in WAT of RAGE knockout mice. In addition, transplantation of adipocyte-RAGE-deleted adipose tissue protected the recipient mice from HFD-induced obesity through upregulation of thermogenic programs and UCP-1 expression in the recipients' native BAT or WAT.[8] Hence, the protective mechanism of RAGE antagonism might be partially due to the induction of browning in WAT, which may have potential therapeutic implications for obesity treatment. The studies conducted in this field are of the animal type in which the RAGE gene is knocked out, and adipose tissue gene expression is used to track the changes in BAT activity. Here, we studied the effects of more subtle dietary AGEs restriction-induced changes in serum levels

of BAT-derived markers, and this may partially explain why we did not observe any associations. In human trials, the most well-established method to measure BAT activity is ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. Since this method is expensive and exposes the individuals to harmful radiation,[44] we measured serum levels of NRG4 and FGF21 as BAT markers that their secretion is increased during browning or BAT activity enhancement.

The analysis of dietary recalls indicated no significant difference in energy intake between the two groups. However, energy intake decreased remarkably in the low-AGEs group at the end of the study compared to the beginning, which partly justifies the weight loss in the low-AGEs group. On the other hand, considering the nonsignificant difference in energy intake between the two groups and the reported relationship between the AGE-RAGE pathway and energy expenditure and the browning process in animal and human studies,[7,8,45] it may be said that the significant weight difference between the two groups is at least in part due to the increase in BAT activity and energy expenditure in the intervention group, which might have been detected by measuring more specific BAT markers and indirect calorimetry. Future prospective trials are recommended to investigate the contribution of AGEs and the potential role of RAGE in this regard.

This study was the first to assess the long-term effects of AGEs restriction on appetite, anthropometric indices, and BAT-derived markers. However, our study had some limitations. Due to the COVID-19 pandemic, we could not measure the participants' energy expenditure by indirect calorimetry. In addition, blinding was not practically possible because of the dietary intervention, and the open-label design increases the risk of biased results. Furthermore, it would be much better if the participants in both groups were provided with their foods as ready-to-eat items or packed food portions throughout the study.

CONCLUSION

Our results showed that dietary AGEs restriction decreased weight and anthropometric indices reflecting visceral adipose tissue in CAD patients. It may also be appropriate for controlling appetite. Since this was possible without a substantial modification in energy intake, the low-AGEs diet may offer a feasible treatment goal of risk reduction in overweight and obese CAD patients.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kozieł P, Jankowski P, Mirek-Bryniarska E, Nessler J, Podolec P, De Bacquer D, *et al*. Obesity in patients with established coronary artery disease over a 20-year period (1997-2017). Pol Arch Intern Med 2021;131:26-32.
2. Cercato C, Fonseca FA. Cardiovascular risk and obesity. Diabetol Metab Syndr 2019;11:74.
3. Brown JD, Buscemi J, Milsom V, Malcolm R, O'Neil PM. Effects on cardiovascular risk factors of weight losses limited to 5-10. Transl Behav Med 2016;6:339-46.
4. Nowotny K, Schröter D, Schreiner M, Grune T. Dietary advanced glycation end products and their relevance for human health. Ageing Res Rev 2018;47:55-66.
5. Kosmopoulos M, Drekolias D, Zavras PD, Piperi C, Papavassiliou AG. Impact of advanced glycation end products (AGEs) signaling in coronary artery disease. Biochim Biophys Acta Mol Basis Dis 2019;1865:611-9.
6. Vlassara H, Uribarri J. Advanced glycation end products (AGE) and diabetes: Cause, effect, or both? Curr Diab Rep 2014;14:453.
7. Song F, Hurtado del Pozo C, Rosario R, Zou YS, Ananthakrishnan R, Xu X, *et al*. RAGE regulates the metabolic and inflammatory response to high-fat feeding in mice. Diabetes 2014;63:1948-65.
8. Hurtado Del Pozo C, Ruiz HH, Arivazhagan L, Aranda JF, Shim C, Daya P, *et al*. A receptor of the immunoglobulin superfamily regulates adaptive thermogenesis. Cell Rep 2019;28:773-91.e7.
9. Alcalá M, Calderon-Dominguez M, Serra D, Herrero L, Viana M. Mechanisms of impaired brown adipose tissue recruitment in obesity. Front Physiol 2019;10:94.
10. Villarroya F, Cereijo R, Villarroya J, Giralt M. Brown adipose tissue as a secretory organ. Nat Rev Endocrinol 2017;13:26-35.
11. Uribarri J, Cai W, Sandu O, Peppa M, Goldberg T, Vlassara H. Diet-derived advanced glycation end products are major contributors to the body's AGE pool and induce inflammation in healthy subjects. Ann N Y Acad Sci 2005;1043:461-6.
12. Anderson GH, Catherine NL, Woodend DM, Wolever TM. Inverse association between the effect of carbohydrates on blood glucose and subsequent short-term food intake in young men. Am J Clin Nutr 2002;76:1023-30.
13. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, *et al*. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110:911- 16.e12.
14. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, *et al*. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498-504.
15. Howell W, Earthman C, Reid P, Delaney J, Houtkooper L. Doubly labeled water validation of the compendium of physical activities in lean and obese college women. Med Sci Sports Exerc 1999;31:S142.
16. Conway JM, Seale JL, Jacobs DR Jr., Irwin ML, Ainsworth BE. Comparison of energy expenditure estimates from doubly labeled water, a physical activity questionnaire, and physical activity records. Am J Clin Nutr 2002;75:519-25.
17. Bergman RN, Stefanovski D, Buchanan TA, Sumner AE,

Reynolds JC, Sebring NG, *et al*. A better index of body adiposity. Obesity (Silver Spring) 2011;19:1083-9.
18. Guerrero-Romero F, Rodríguez-Morán M. Abdominal volume index. An anthropometry-based index for estimation of obesity is strongly related to impaired glucose tolerance and type 2 diabetes mellitus. Arch Med Res 2003;34:428-32.
19. Mark AB, Poulsen MW, Andersen S, Andersen JM, Bak MJ, Ritz C, *et al.* Consumption of a diet low in advanced glycation end products for 4 weeks improves insulin sensitivity in overweight women. Diabetes Care 2014;37:88-95.
20. Macías-Cervantes MH, Rodríguez-Soto JM, Uribarri J, Díaz-Cisneros FJ, Cai W, Garay-Sevilla ME. Effect of an advanced glycation end product-restricted diet and exercise on metabolic parameters in adult overweight men. Nutrition 2015;31:446-51.
21. Uribarri J, Cai W, Ramdas M, Goodman S, Pyzik R, Chen X, *et al.* Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: Potential role of AGER1 and SIRT1. Diabetes Care 2011;34:1610-6.
22. Cai W, He JC, Zhu L, Peppa M, Lu C, Uribarri J, *et al.* High levels of dietary advanced glycation end products transform low-density lipoprotein into a potent redox-sensitive mitogen-activated protein kinase stimulant in diabetic patients. Circulation 2004;110:285-91.
23. Sohouli MH, Sharifi-Zahabi E, Lari A, Fatahi S, Shidfar F. The impact of low advanced glycation end products diet on obesity and related hormones: A systematic review and meta-analysis. Sci Rep 2020;10:22194.
24. Hall KD, Ayuketah A, Brychta R, Cai H, Cassimatis T, Chen KY, *et al.* Ultra-processed diets cause excess calorie intake and weight gain: An inpatient randomized controlled trial of *ad libitum* food intake. Cell Metab 2019;30:67-77.e3.
25. Unoki H, Yamagishi S. Advanced glycation end products and insulin resistance. Curr Pharm Des 2008;14:987-9.
26. Kellow NJ, Coughlan MT. Effect of diet-derived advanced glycation end products on inflammation. Nutr Rev 2015;73:737-59.
27. Sergi D, Boulestin H, Campbell FM, Williams LM. The role of dietary advanced glycation end products in metabolic dysfunction. Mol Nutr Food Res 2021;65:e1900934.
28. Luévano-Contreras C, Garay-Sevilla ME, Wrobel K, Malacara JM, Wrobel K. Dietary advanced glycation end products restriction diminishes inflammation markers and oxidative stress in patients with type 2 diabetes mellitus. J Clin Biochem Nutr 2013;52:22-6.
29. Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, *et al.* The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: Sex and race differences. Obesity (Silver Spring) 2011;19:402-8.
30. Frankenfield DC, Rowe WA, Cooney RN, Smith JS, Becker D. Limits of body mass index to detect obesity and predict body composition. Nutrition 2001;17:26-30.
31. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
32. VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free mass and fat mass: Potentially useful indicators of nutritional status. Am J Clin Nutr 1990;52:953-9.
33. Wells JC, Williams JE, Fewtrell M, Singhal A, Lucas A, Cole TJ. A simplified approach to analysing bio-electrical impedance data in epidemiological surveys. Int J Obes (Lond) 2007;31:507-14.
34. Liu P, Ma F, Lou H, Liu Y. The utility of fat mass index versus body mass index and percentage of body fat in the screening of metabolic syndrome. BMC Public Health 2013;13:629.
35. Lokpo SY, Amenyega W, Doe P, Osei-Yeboah J, Owiredu WK, Obirikorang C, *et al.* Abdominal volume index is a better predictor of visceral fat in patients with type 2 diabetes: A cross-sectional study in Ho municipality, Ghana. Alex J Med 2022;58:85-91.
36. Wu L, Zhu W, Qiao Q, Huang L, Li Y, Chen L. Novel and traditional anthropometric indices for identifying metabolic syndrome in non-overweight/obese adults. Nutr Metab (Lond) 2021;18:3.
37. Chin YT, Lin WT, Wu PW, Tsai S, Lee CY, Seal DW, *et al.* Characteristic-grouped adiposity indicators for identifying metabolic syndrome in adolescents: Develop and valid risk screening tools using dual population. Nutrients 2020;12:3165.
38. de Courten B, de Courten MP, Soldatos G, Dougherty SL, Straznicky N, Schlaich M, *et al.* Diet low in advanced glycation end products increases insulin sensitivity in healthy overweight individuals: A double-blind, randomized, crossover trial. Am J Clin Nutr 2016;103:1426-33.
39. Harcourt BE, Sourris KC, Coughlan MT, Walker KZ, Dougherty SL, Andrikopoulos S, *et al.* Targeted reduction of advanced glycation improves renal function in obesity. Kidney Int 2011;80:190-8.
40. Perrone A, Giovino A, Benny J, Martinelli F. Advanced glycation end products (AGEs): Biochemistry, signaling, analytical methods, and epigenetic effects. Oxid Med Cell Longev 2020;2020:3818196.
41. Sebeková K, Klenovics KS, Boor P, Celec P, Behuliak M, Schieberle P, *et al.* Behaviour and hormonal status in healthy rats on a diet rich in Maillard reaction products with or without solvent extractable aroma compounds. Physiol Behav 2012;105:693-701.
42. Poulsen MW, Bak MJ, Andersen JM, Monošík R, Giraudi-Futin AC, Holst JJ, *et al.* Effect of dietary advanced glycation end products on postprandial appetite, inflammation, and endothelial activation in healthy overweight individuals. Eur J Nutr 2014;53:661-72.
43. Havel PJ. Peripheral signals conveying metabolic information to the brain: Short-term and long-term regulation of food intake and energy homeostasis. Exp Biol Med (Maywood) 2001;226:963-77.
44. Andersson J, Lundström E, Engström M, Lubberink M, Ahlström H, Kullberg J. Estimating the cold-induced brown adipose tissue glucose uptake rate measured by (18) F-FDG PET using infrared thermography and water-fat separated MRI. Sci Rep 2019;9:12358.
45. Popp CJ, Zhou B, Manigrasso MB, Li H, Curran M, Hu L, *et al.* soluble receptor for advanced glycation end products (sRAGE) Isoforms predict changes in resting energy expenditure in adults with obesity during weight loss. Curr Dev Nutr 2022;6:nzac046.